Naval Medical Research Unit Dayton
Wright-Patterson AFB, Ohio

Science Update

Volume 5, Issue IV Fall

MISSION

To maximize warfighter performance and survivability through premier aeromedical and environmental health research-delivering solutions to the field, the Fleet, and for the future.

VISION

NAMRU-D is Navy Medicine's world class, global aeromedical and toxicology research leader. Our efforts and innovative products are aligned with operational requirements to solve the naval and joint warfighter challenges of the future.

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Flying in the Dark? NAMRU-D's Night Vision Simulation Laboratory to Benefit Aviators

Night Vision Simulation Laboratory housed at Naval Medical Research Unit Dayton aims to develop training scenarios for the next generation of aviation training devices.

By: LCDR Dustin Huber

We sometimes take our five senses for granted, especially our vision. As our most utilized sense, vision gives us accurate information about our environment, where we are within it, and how it changes as we move. Most don't give this sense a second thought, until our vision is degraded.

Imagine driving a familiar route in the daylight hours, under a clear blue sky. Now picture that same drive under the cover of darkness with a heavy fog or snow shower. Your dashboard, or "cockpit", hasn't changed, other than being lit up. The road ahead no longer looks familiar. Landmarks may be invisible. Attempting to navigate your car via GPS and your console alone seems unthinkable. This is what our aviators do every night!

Although aviators are aided by the most sophisticated night vision technology in the world, there are significant hazards to flying at night, specifically with what we can and cannot see. For example, on dark nights pilots may find themselves descending towards a runway over water or surrounded by darkness. Without other lights or cues from the earth or sky to give them visual cues, they may mistakenly change to an unsafe descent, potentially leading to a mishap. To combat this, Naval Aviation rigorously trains aircrew in both the instrument flight of their aircraft (literally, flying by "dashboard" alone) and in the pitfalls of over-reaching our visual capabilities at night.

Now, the Naval Medical Research Unit Dayton (NAMRU-D) at Wright-Patterson Air Force Base, Ohio offers a brand new capability in their new Night Vision Simulation Laboratory to combat degraded vision environments by addressing and expanding on this second aspect of training. Scientists at NAMRU-D use a simulator that is compatible with night vision technology, to investigate illusions and visual problems unique to the night environment.

The goal is to develop training and scenarios for the next generation of training devices. We know by providing high quality training to aviators in extreme environments, their ability to fly missions effectively and safely improve. That is a win for NAMRU-D, Naval Aviation and the aircrew we strive to protect!

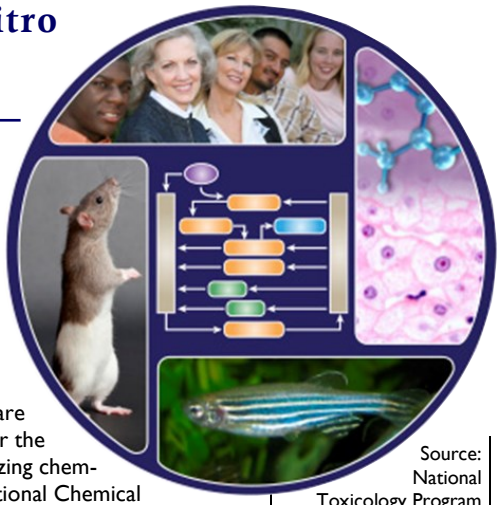
This work would not be possible without the support of U.S. Navy Air Systems Command (NAVAIR) PMA-205, Renaissance Sciences Corp, and Naval Air Warfare Center Training Systems Division (NAWCTSD).

Evaluation of Pharmacokinetic Models for In Vitro to In Vivo Extrapolation of High Throughput Toxicity Screening Data

By: Dr. Lisa Sweeney

Emerging approaches in human health risk assessment rely on determination of biologically-effective concentrations in suites of in vitro high throughput screening (HTS) assays. In order to compare human exposure to *in vitro* biologically effective doses, pharmacokinetic models may be used to calculate the exposure levels required to yield internal chemical doses equivalent to the levels of concern. Internal dosimetry is computed either from validated *in vitro* models or predicted from relatively simplistic models parameterized via in silico predictive algorithms and limited *in vitro* data.

In preparation for a February 2016 workshop, U.S. EPA and the National Institute of Environmental Health Sciences are offering a series of webinars on the use of In Vitro to In Vivo Extrapolation (IVIVE) for chemical screening and risk decision making. Because of the importance of pharmacokinetic models in IVIVE, Dr. Lisa Sweeney, Senior Scientist in the Environmental Health Effects Directorate at NAMRU-D was invited to present on the topic of model evaluation. The importance of understanding the contexts in which the models are to be applied was stressed. A model that is "adequate" for a screening approach, such as prioritization, might not be adequate for higher-stakes applications, such as the establishment of an occupational exposure limit. It was recommended that the following model characteristics be evaluated: the realism and suitability of the structure, the accuracy of the mathematical implementation, ability to predict the available data), and the suitability of the parameter values. A case study of the relatively simplistic pharmacokinetics models parameterized with limited in vitro data (such as metabolism in cultured human liver cells and binding to blood plasma proteins) was presented. Dr. Sweeney concluded that these simplistic models are likely adequate for the purpose of prioritizing chemicals in the International Chemical Safety for Sustainability (iCSS) Dashboard databases for more in-depth evaluation. The iCSS Dashboard (http://actor.epa.gov/dashboard/) provides access to the results of more than 800 HTS in vitro assay endpoints for over 1800 chemicals, including those from the Toxicity Forecaster (ToxCast) project and the federal Toxicity Testing in the 21st century (Tox21) collaboration.



Source: National Toxicology Program U.S. Department of Health and Human Services

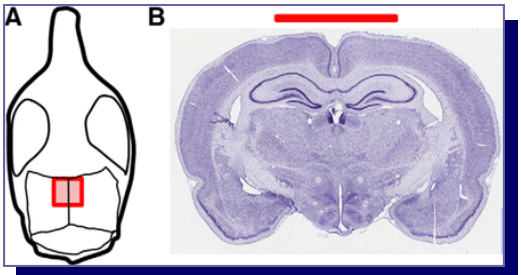
On-going efforts in IVIVE research are expected to better delineate the limitations of these models, lead to strategies for their improvement, and potentially expand the domain of their application in risk assessment. Slides and webinar recordings for the series are currently available or will be made available at National Toxicology Program Public Health webpage.

NAMRU-D Research Highlighted by the Journal of Neuroscience

By: Dr. Karen L. Mumy

Research performed by scientists from the Environmental Health Effects Directorate of the Naval Medical Research Unit Dayton (NAMRU-D) was prominently featured in the Society for Neuroscience's Journal of Neuroscience. NAMRU-D's Dr. Joyce Rohan, Mr. Shawn McInturf and Ms. Molly Miklasevich were part of a collaborative research team that also included Drs. Ryan Jankord and Kim Carhuatanta of the Air Force Research Laboratory, 711th Human Performance Wing.

The team utilized a rat model to study, the effects of electrical stimulation, specifically transcranial direct current stimulation (tDCS). tDCS employs the use of an electrical current to alter neural activity and impact brain function. In order to stimulate the brain, electrodes were surgically placed on the top of the scalp of the rats and electrical current was provided while the animals were awake and freely moving. After electrical stimulation, the brains were quickly removed and various types of activity in certain areas of the brain, such as the hippocampus, were recorded for many hours following stimulation.



Electrode placement showing approximate size and placement on the rat skull. **A**, Drawing of rat skull to demonstrate the positioning of the electrode in our experimental setup. The electrode was centered on the sagittal suture and ran from 0.0 to −5.0 mm caudal to bregma. **B,** The Nissi-stained image (Mikula et al., 2007) shows a coronal tissues section close to the center of the electrode.

Together, the research team published an article in the 16 September 2015 issue of the Journal of Neuroscience. Overall, the team found that 30 minutes of brain stimulation in rats enhanced synaptic plasticity, a neuronal process crucial for learning and memory. This effect was still detectable up to 24 hours after stimulation. Deciphering such activities on a molecular level will ultimately lead to a better understanding of the mechanisms by which brain stimulation produces its effects on cognition and performance.

The article, entitled "Modulating Hippocampal Plasticity with In Vivo Brain Stimulation", was one of two articles chosen by the editors to be highlighted in "This Week in The Journal" for the Journal of Neuroscience. Dr. Teresa Esch, who wrote the feature on the article, emphasized that one of the most important findings of the study was the fact that the research team determined that some of the tDCS stimulated effects can be detected in brains as much as 24 hours post-stimulation, which should "simplify future investigations into the cellular mechanisms underlying the effects of tDCS."

The article is free to the public at http://www.jneurosci.org/content/35/37/12824.full. It was also chosen to be featured on "Neuronline", an online component of the Journal of Neuroscience.

Recent Developments in Triservice Aeromedical Research

By: Dr. Richard Arnold

There has been tremendous growth in joint Navy-Air Force aeromedical research in recent years at Wright-Patterson AFB. And, in 2015 a new mechanism to further enhance joint research in aerospace medicine was implemented under the auspices of the Defense Health Agency Joint Programming Committee 5 (JPC-5). Under a new JPC-5 working group for research in "Aviation Mishap Prevention and Aircrew Health" NAMRU-D, US Army Aeromedical Research Laboratory (USAARL), and USAF School of Aerospace Medicine (USAFSAM) are engaged in seven new joint research projects to address some of the most prevalent threats to the health and safety of US military pilots and flight crew.

Across the military services aviation mishaps account for between 50 and 100 service member deaths in a typical year, and in the Navy alone they account for approximately 75% of the service-wide financial losses attributable to mishaps or accidents. Approximately 75% of aviation mishaps are due to human factors or aeromedical causes, and foremost among these - by far - is pilot spatial disorientation (SD).

Accordingly, research to understand and mitigate pilot SD receives significant support in the new JPC-5 sponsored program. Dr. Henry Williams of NAMRU-D is leading a NAMRU-D/USAARL/USAFSAM project to develop and validate integrated visual, vestibular, and \cognitive models of SD to inform subsequent mitigation approaches such as improved pilot selection, training, or cockpit engineering approaches.

A USAARL-led project focusing specifically on mitigations for rotary wing brownout illusion, the most prevalent form of SD in helicopters, is also a triservice effort, with researchers from NAMRU-D and USAFSAM supporting the project. These fresh initiatives in SD research will support and be supported by new facilities at WPAFB, specifically NAMRU-D's one of a kind Disorientation Research Device (DRD), a unique six axis of motion dynamic motion device that provides realistic visual and acceleration conditions of flight. The new program is also supporting research into aviation-related hypoxia and Decompression Sickness (DCS), and spinal pain and injury related to the flight environment. The former research is being executed by USAFSAM and NAMRU-D in collaboration, while the latter is led by USAARL, with support from USAFSAM and NAMRU-D.

This triservice initiative is supporting important research in a domain that has been relatively neglected by all of the services in recent years, despite mishap and injury statistics that demonstrate a great need for attention. It is encouraging that leaders in joint medical research have recognized this gap. With the reinvigorated triservice focus on the problem efforts to mitigate aeromedical threats will benefit from cross-service alignment, coordination, and collaboration, which will ultimately return better solutions to the warfighter and better value to the research sponsor.

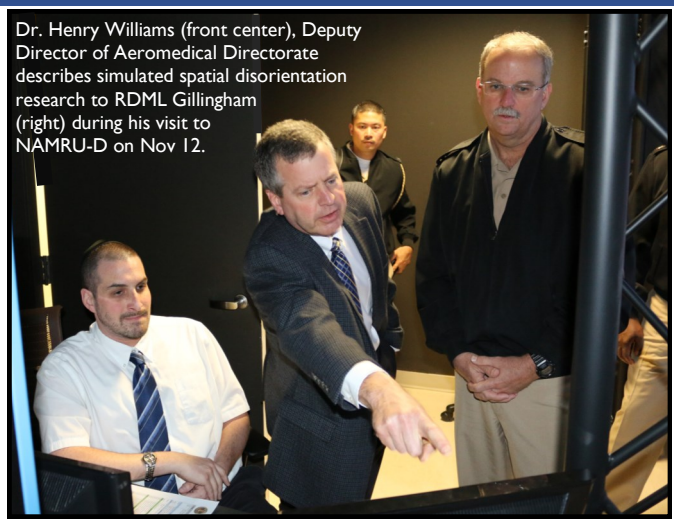
Navy Medicine West Rear Admiral Visits and Meets with NAMRU-D

By: NAMRU-D Public Affairs

Naval Medical Research Unit Dayton saluted RDML Bruce Gillingham, Navy Medicine West (NMW) Commander on November 12 as a part of the RDML's worldwide command tour to all eight Navy Medicine Research & Development Enterprise facilities.

CAPT Jeffrey Andrews, Commanding Officer, NAMRU-D and CAPT Rees Lee, Executive Officer, NAMRU-D provided a command brief to get things started. Dr. Michael Gargas, Toxicology Director and Dr. Richard Arnold, Aeromedical Director attended and spoke on their respective directorates' mission and core capabilities.

Following the brief, Gargas and Arnold led RDML Gillingham on tours of NAMRU-D's scientific laboratories. Aeromedical highlights included hypoxia program, vision sciences, motion sickness countermeasures, fatigue countermeasures, spatial disorientation mitigation, and the Disorientation Research Device. The Environmental Health Effects highlights included inhalation exposure labs, neurobehavioral, neurophysiology, *in-vitro*, and specialized exposures systems labs. To further emphasize NAMRU-D's initiative to align research efforts to solve warfighter challenges, CAPT Andrews arranged for the RDML to meet with our co-located 711th Human Performance Wing (HPW) Commander, Brigadier General Timothy Jex. During which, insight for both administrative operations and research operations were obtained.

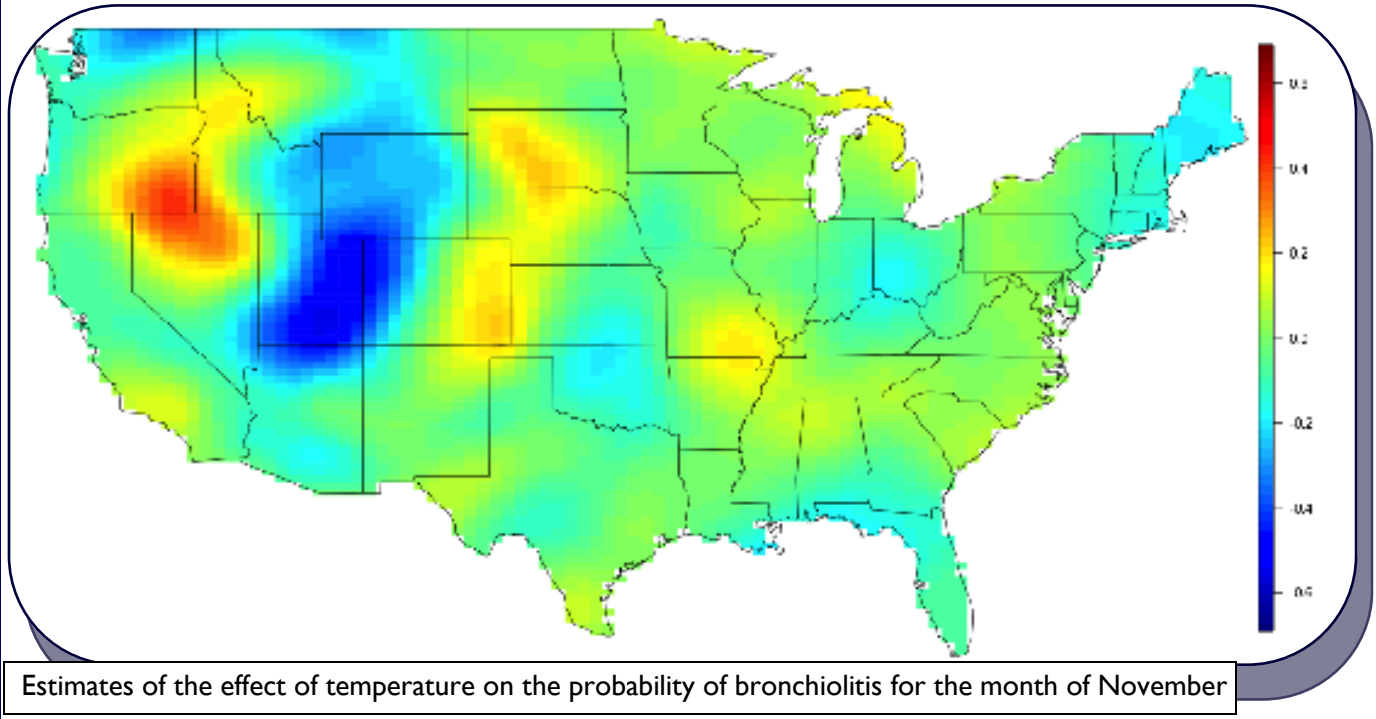


Dr. Henry Williams (front center), Deputy Director of Aeromedical Directorate describes simulated spatial disorientation research to RDML Gillingham (right) during his visit to NAMRU-D on Nov 12.

The 711 HPW supported four lab tours for the NMW group including The Battlefield Air Targeting Man Aided kNowledge (BATMAN), and USAF School of Aerospace Medicine's Centrifuge, Altitude Research Chambers, and Centers for Sustainment of Trauma And Readiness Skills. All continue to present potential future collaboration.

To close the visit, RDML Gillingham called an All Hands to discuss the role NMW will have with NAMRU-D and opened the floor for any and all questions from NAMRU-D staff. The open forum presented a great deal of respect towards all members of the NAMRU-D family. Overall, the visit went exceptionally well and built a good foundation for the Navy Medicine West—NAMRU-D partnership.

Using the MHS Data Repository to Trace the Environmental Factors Affecting the Spread of Respiratory Syncytial Virus



Estimates of the effect of temperature on the probability of bronchiolitis for the month of November

By: CAPT Rees "Chip" Lee

Respiratory Syncytial Virus (RSV) causes 50-80 percent of the infant bronchiolitis cases in the United States, hospitalizes 3.4 million children under the age of 5 annually worldwide and kills 200,000 children every year, with over 500 deaths in the U.S. Unfortunately, there is no completely effective treatment for bronchiolitis. In the absence of an effective treatment, understanding the key factors influencing the spread of this deadly virus is paramount.

Our team of Navy investigators, including myself, a Pediatric Pulmonologist, and scientists from Vanderbilt University and Brigham Young University analyzed the impact of temperature and humidity on the spread of RSV. Obtaining the requisite national view of the illness was imperative when considering large climatic changes. The disjointed patchwork of state and private medical systems made use of civilian databases an impossible challenge. By contrast, the military has a truly national healthcare system with a centralized database capable of such analyses. With almost 10 million beneficiaries of all ages, the Military Healthcare System Data Repository (MDR) is the largest cradle-to-grave national medical database in the U.S. Its unique national scope presents research capabilities available nowhere else.

Using the MDR, the annual march of bronchiolitis from the Southeastern U.S. to the Pacific Northwest was plotted based on the spatiotemporal characteristics of over 125,000 cases. The team used data from the National Climatic Data Center and was able to demonstrate that temperature and humidity did influence bronchiolitis rates with the impact being most pronounced at the start and end of epidemics.

While the emergence and termination of viral pathogens in a community are likely impacted by multiple factors, studies such as this bring us closer to a fuller understanding of how this disease acts in a population.

Our research results are to be published in the journal Emerging Infectious Diseases.

The study demonstrated the power of the MDR to address medical research questions of a national scope. While the research potential of the MDR has long been recognized, acquiring the required permissions, funding, and expert personnel have prevented any significant research.

In 2008, a public-private partnership between the Navy and the research firm HealthResearchTX attempted to crack this nut. Together with Capt. Paul Rockswold from the Navy and Marine Corps Public Health Center, I served as the government sponsor for this research collaboration, the Health Outcomes Research Center of Excellence (HORCE).

This partnership has brought military physicians and researchers together with academic and industry partners to answer significant medical questions important to military medicine and the U.S. population.

To date, HORCE has supported military principal investigators on 46 protocols. In 2014-2015, there were over 50 publications on topics ranging from hemophilia to cardiovascular disease; hip/knee replacement to neurologic diseases. Navy residents and fellows have used HORCE for their graduate studies.

At NAMRU-D, the MDR is being used by Lt. Cmdr. John Bradley, Research Optometrist, to explore eye disease and Lt. Cmdr. Mike Tapia, Aviation Physiologist, to investigate spinal disorders in aviators.

The potential is endless for the MDR and HORCE to answer the important clinical questions which change how we practice medicine. It is extraordinarily exciting to be involved in this initiative.

Navy Medicine R&D Enterprise Leadership Meet in Dayton

By: NAMRU-D Public Affairs

Naval Medical Research & Development Enterprise Leadership Meeting held in Dayton, Ohio, 21-23 October 2015 at Wright-Patterson Air Force Base.

The Naval Medical Research Unit Dayton (NAMRU-D) hosted the annual Navy Medicine Research and Development (R&D) Enterprise Leadership Meeting October 21-23 2015 at Wright-Patterson Air Force Base in Dayton, Ohio.

Navy Medicine's diverse R&D laboratory leadership, science directors, and key administrative support from all eight Continental United States (CONUS) and Outside the Continental United States (OCONUS) laboratories came together in the cardinal state to discuss developments, challenges, and target future planning requirements.

NAMRU-D Commanding Officer CAPT Jeffrey Andrews said this meeting is "the perfect forum for leaders to exchange ideas and learn how to make our commands unified towards R&D efforts and internal processes that have value making our products and operations better. Common challenges and successes can be discussed and future vision and strategy developed." During the three-day gathering, focus was on the labs top five challenges, Infectious Diseases Threat Prioritization, Emerging Diseases Risk Management, and administrative support items. Working groups and breakout sessions were used to better identify ways to enhance how to do business while meeting the mission requirements. "The face to face and personal meetings with each other allowed candid and open discussion. This was critical to expediting process improvement and decision making," said CAPT Andrews.

The Naval Medical Research Center's (NMRC) Commanding Officer, CAPT Jacqueline Rychnovsky, kicked off the meeting by saying "advantages and disadvantages are and should be transparent," which opened the discussion to frame accomplishments and concerns to present to the Navy Medicine West (NMW) Commander, RDML Bruce Gillingham the second day of the meeting via teleconference call.

After all attendees introduced themselves to the RDML CAPT Rychnovsky stated, "[We] would like to share our top concerns with you; some with and some without solutions." The top five concerns presented were 1) Support agreements, 2) Funding model, 3) Fiscal audit impact, 4) Human resource transitions, and 5) Conference approval timeline. Following the discussion RDML Gillingham was positive and plans to brief Surgeon General on Navy Medicine R&D once he has visited all eight NMR&D laboratories. NMR&D leadership plans to focus on strengths to frame each solution approach. RDML Gillingham closed with, "Looking forward to being joined at the hip!"

Additionally, Brigadier General Timothy Jex, Commander of the 711th Human Performance Wing (711 HPW) addressed NMR&D enterprise leadership prior to speaking with RDML Gillingham. The Commander's brief provided exceptional perspective on how their research is strategically modeled and highlighted the jointness between the Wing and NAMRU-D, both in Dayton and the San Antonio lab.

Meeting attendees were given a tour of NAMRU-D Toxicology and Aeromedical Research Directorate as well as a visit to a few 711 HPW lab areas. This emphasized the unique research capabilities made possible on a joint base such as Wright-Patterson AFB.

When asked what the successes of this year's meeting was CAPT Andrews said, "collaboration and networking combined with creative brainstorming resulted in recommendations to the Commanding Officer, NMRC to further refine the enterprise vision and mission. Speed to decision and coherence was emphasized with collective support from all command leaders. Issues were clearly identified and expectations defined with a way forward that enables teamwork, cross-lab collaboration, total jointness, and robust process improvement."

NAMRU-D & USAFSAM Set a High Bar for Joint Research

Dr. Jeffrey Phillips, Principal Investigator, NAMRU-D describes how the Reduced Oxygen Breathing Device (ROBD) is used as a training modality. NAMRU-D and USAFSAM have teamed up to evaluate the differences between the ROBD, Reduced Oxygen Breathing Environment (ROBE), and hypobaric chamber hypoxia familiarization training (HAT).

By: Dr. Jeffrey Phillips

Hypoxia is still a major risk to the safety of aircrew and operational readiness across the Department of Defense (DoD) aviation commands. Aviation systems are not equipped with full-proof hypoxia detection and warning instrumentation to warn aircrew when hypoxia is eminent. Therefore aircrew receive hypoxia familiarization training (HAT) so that they are equipped to recognize their individual symptoms of hypoxia so they can initialize emergency procedures before they become incapacitated.

Since the 1940s HAT has been conducted in hypobaric chambers that work by reducing the partial pressure of oxygen to create a controlled equivalent to the environment flight crew experience during a rapid depressurization or a life support equipment failure. Although hypobaric chambers have served as the primary modality for HAT for over 60 years, chambers are expensive to maintain, there is a limit to the number of chambers available, and they may be associated with subtle decompression injuries that have gone undetected until recently.

In order to reduce the expense of HAT, and to reduce the risk of decompression injury the Navy and Air Force are utilizing two normobaric training modalities (Reduced Oxygen Breathing Environment*; ROBE and the Reduced Oxygen Breathing Device; ROBD) to subsidize or replace hypobaric chamber HAT. Both the ROBD and the ROBE do not alter the barometric environment that trainees experience thus eliminating the risk of training related decompression injuries. The ROBE and ROBD simply reduce the concentration of oxygen received by the trainee. The ROBD delivers hypoxia air mixtures through a standard aviation mask and is intended for tactical operators who wear a mask in-flight. The ROBE is a large sealed plastic room that is filled with nitrogen to train non mask wearing aircrew.

Although the ROBE and ROBD are cheaper to acquire, maintain and eliminate the risk of decompression injuries, many have questioned the validity of using these forms of normobaric hypoxia in training as a proxy for hypobaric training (hypobaric chamber). To address this important question the NAMRU-D hypoxia team has teamed with the United States Air Force School of Aviation Medicine (USAFSAM) to perform a thorough evaluation of differences between the three training modalities. Thirty research participants will be placed in each of the three training modalities to directly compare cognitive performance effects and symptom presentation across the three modalities. Data collection began this past summer (2015) and is scheduled to be completed in the spring of 2016.

The combined effort of the Air force and Navy to address the questions is another example of cross service collaboration to address a common question as well as an example of how research at the Harry Armstrong Complex at Wright-Patterson AFB benefits both policy and the welfare of the warfighter across the DoD.

**Check out the previous NAMRU-D Science Update "Introducing the Reduced Oxygen Breathing Environment (ROBE) at NAMRU-D" at http://www.med.navy.mil/sites/nmrc/Documents/Newsletter/NAMRU-D%20Science%20Update%20Vol_V_Iss_IIIreduced.pdf*

NAMRU-D Products & Presentations

Folga, R.V. (Nov, 2015). Update on the disorientation research device at Naval Medical Research Unit Dayton. Aerospace *Physiology Society's White Matter Chronicles*, Edition 2

Kuempel, E.C., Sweeney, L.M., Morris, J.B., & Jarabek, A.M. (Nov, 2015). Advances in inhalation dosimetry models and methods for occupational risk assessment and exposure limit derivation. *Journal of Occupational and Environmental Hygiene, 12 (1),* 18-40. <http:// dx.doi.org/10.1080/15459624.2015.1060328>.

Rohan, J.G., Carhuatanta, K.A., McInturf, S.M., Miklasevich, M.K., & Jankord, R. (Oct, 2015). Modulating hippocampal plasticity with in-vivo brain stimulation. Presentation at Society of Neuroscience Meeting, Chicago, Illinois.

Sweeney, L.M. (Nov, 2015). Evaluation of pharmacokinetic models for the disposition of lead (Pb) in humans, in support of application to occupational exposure limit derivation (Report Number NAMRU-D-16-11). Technical Report retrieved from Defense Technical Information Center.

Sweeney, L.M. (Dec, 2015). In vitro to in vivo extrapolation (IVIVE) for high-throughput prioritization and decision making: the role of pharmacokinetic model evaluation. Webinar presentation at National Toxicology Program/EPA Series.

Williams, H.P. & Patterson, F.P. (Oct, 2015). Spatial disorientation: Pilot spatial strategies and visual illusions. Presentation at 711th Human Performance Wing Tech Day, Wright-Patterson Air Force Base, Ohio.

Commanding Officer's Corner

Captain Jeffrey M. Andrews, MSC, USN
Commanding Officer

Time flies when you are having fun and becoming the global leader in aeromedical and toxicology research. The fun is only a result of the passion and pride of our researchers and support staff who continue to surge forward despite significant transitions and fiscal challenges. Since the inception of our command in October 2010, NAMRU-Dayton's short history is distinguished and filled with impressive accomplishments and unprecedented milestones. The end of 2015 was a busy time marked by major events. First, NAMRU-Dayton was proud to host the Navy Medicine Research & Development Leadership Enterprise meeting in October where leaders were able to meet and brainstorm the future of Navy Medical Research and Development. You can read more about the specifics of this meeting later in this newsletter. The next event was a visit by Navy Medicine West Commander, RDML Gillingham, which proved to be very productive and educational. Shortly after this visit, the 4th Annual Open House and first Technical day occurred and served as a one stop shop for knowledge and educational outreach with an open exchange of ideas and prime opportunity for networking and collaboration between the USAF 711th Human Performance Wing and us.

NAMRU-Dayton was then visited by the BUMED Field Support Activity to conduct a spot check on audit readiness compliance and financial areas for improvement. The last but certainly not least events of 2015 included major updates to our inhalation facilities, international visits by our staff to Israel and India with likely collaborative research projects in the near future, and the last phase of acceptance testing of the Disorientation Research Device with a long awaited delivery projected before the new year. In addition to these external events and visits, the daily routine and completion of a myriad of science projects and innovative research continues to be the focus of our efforts.

As I reflect on the past, present, and future of NAMRU-D and our Navy R&D enterprise, I extend my gratitude for the support of our higher chain of command and my sincere appreciation to the NAMRU-D team for their dedication, loyalty and unsurpassed professionalism. Happy New Year to all!

Taking the Helm of Navy Medicine's Aeromedical & Environmental Health Research

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